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RESEARCH ARTICLE

Anti-inflammatory Activity of 1-Substituted Glyoxal β-Carboline Derivatives

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Abstract The anti-inflammatory properties of β-carbolines have been widely studied, highlighting their potential in treating inflammatory disorders. This research investigates the anti-inflammatory activity of selected 1-substituted glyoxal β-carboline derivatives, achieved through a one-step conversion of 5-hydroxy-L-tryptophan with activated glyoxal, without forming tetrahydro-β-carboline (THβC) intermediates. These derivatives (**4e-g**) were synthesized successfully without requiring expensive metal catalysts, prolonged reaction times, or stringent reaction conditions, and yielded moderate amounts. Our findings indicate that all the derivatives significantly inhibit xanthine oxidase (XO) activity, leading to a reduction in reactive oxygen species (ROS) and free radicals. This inhibition disrupts the inflammatory cascade and attenuates the inflammatory response.

Keywords: 1-Substituted β-carboline, Activated glyoxal, L- Tryptophan, Anti-inflammatory, Xanthine oxidase (XO).

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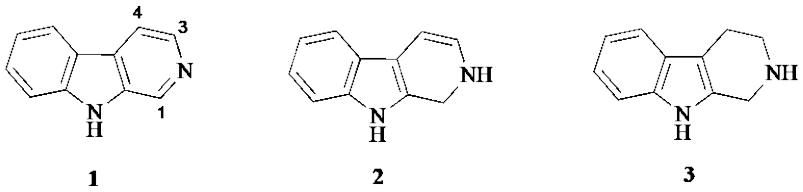
Introduction

For decades, β-Carboline (βCs) was known for its abundance in natural resources with medicinal purposes. They can be isolated from plants, marine creatures, microbes, insects, food, alcoholic drinks, tobacco smoke, and human tissues as well as body fluids [1]. βCs was reported to have biological properties including sedative, anxiolytic, hypnotic, anticonvulsant, anticancer, antiviral, antiparasitic, and antibacterial activity. βCs also have a powerful potential for the therapy of Alzheimer's disease (AD), Parkinson's disease (PD), depression, and other central nervous system (CNS) illnesses [1]. Numerous investigations on βCs have demonstrated the remarkable range of biological activities exhibited by these organic substances [2]. Thus, its potential therapeutic activities are very much aligned with the varied health benefits as described [3].

The saturation of the N-containing 6-membered ring is used to further classify βCs (pyridine ring) (Figure 1). Fully aromatic β-Carbolines (FAβCs) **1** are unsaturated pyridine ring containing compounds, while partially and fully saturated compounds are known as 3,4-dihydro-β-carbolines (DHβCs) **2** and tetrahydro-β-carbolines (THβCs) **3**, respectively [4]. As shown in Figure 2, norharmane, harmane, and harmine are the most well-known natural compounds that have the main skeleton of β-carboline and were reported to have biological or toxicological action such as antidepressant, hallucinogenic, tremorgenic, hypotensive or cardiovascular actions, and psychotropic properties [5, 6].



1 **2** **3**

Figure 1. Classification of β-carbolines: (**1**) FaβCs, (**2**) DHβCs and (**3**) THβCs

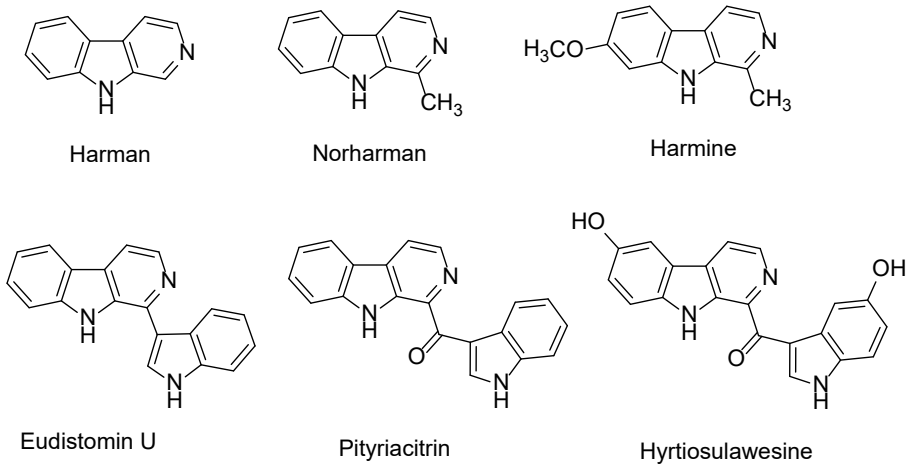


Figure 2. The chemical structures of β-carboline

It has also been reported that the medicinal activities of β-carbolines were improved by the introduction of appropriate substitution at C-1 of βCs [2]. Pityriacitrin for example, a rare marine β-carboline alkaloid with an indole ring connected to a carbonyl group on the C-1 position, caught researchers' interest because of its unusual structure and extensive UV absorption [7]. Pityriacitrin was primarily discovered in a marine bacterium of the *Paracoccus* genus by Nagao *et al*. in 1999 [8]. This compound has been discovered to exhibit a wide range of biological functions, as well as excellent anti-inflammatory, antitumor activity and cytotoxicity [8]. Besides that, pityriacitrin and its derivatives were also reported to have good antimalarial activity against a chloroquine-resistant strain of *Plasmodium falciparum* (FcB1) [9].

Eudistomins U is another class of 1-substituted-β-carbolines alkaloids found in *Ascidians Sea* with a structurally diverse and show wide-ranging biological activities. Some of the well-known bioactivities include antimicrobial, antioxidant, antimalarial and anticancer properties [10]. Hyrtiosulawesine (Figure 2), on the other hand, is also a derivative of 1-substituted β-carboline [11]. This chemical was identified in Indonesian sea sponges and is called *Hyrtios erectus*. According to Zulkifli *et al*., biological studies of hyrtiosulawesine demonstrated anticancer, antioxidant, antiplasmodial, anti-inflammatory, and antidiabetic effects. Furthermore, this marine alkaloid was discovered to have an antiproliferative effect on human nasopharyngeal carcinoma epithelial cells [12].

Given that numerous β-carbolines are recognize for their anti-inflammatory properties, this study examines the anti-inflammatory effects of certain synthesized 1-substituted glyoxal β-carboline derivatives. The Pictet-Spengler reaction was adopted to be the most effective technique to form the β-carbolines ring system via C-C bond formation with tryptophan as the starting material [13]. In general, an iminium salt is formed via the acid-catalyzed condensation of tryptophan and tryptamine derivatives with aldehydes. Then endo cyclization occurs between a carbon nucleophile of a sufficiently reactive aromatic moiety and the activated iminium ion, resulting in an N-heterocyclic ring via a new C-C bond [14]. According to Ash'ari *et al*.'s 2022 study, intermediates (**3**) are obtained through Pictet-Spengler cyclization, followed by aromatization to produce the β-carboline ring moiety [2]. Therefore, in this study, we describe the synthesis of 1-substituted glyoxal β-carboline derivatives using 5-hydroxy-L-tryptophan as the starting material and evaluate their potential in anti-inflammatory properties.

Materials and Methods

General

Commercially available reagents were used as supplied by Sigma-Aldrich and Biotek Abadi Sdn. Bhd, without further purification, unless stated otherwise. Air and sensitive compounds were stored in a desiccator over self-indicating silica pellets, under nitrogen atmosphere. Column chromatography was carried out using Merck 9385 Kieselgel 60 (230-400 mesh ASTM) and hand bellows were used to apply pressure to the column. Analytical thin-layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF254. Plates were visualized under UV light (at 254 nm), stained with potassium permanganate solution followed by heating, or exposing to iodine vapor. Fourier Transformed Infrared absorption spectra were recorded on Varian 3100 excalibur series instruments Spectrum 2000 or Spectrum One, both in the spectral range of 4000 to 400cm-1. The molecular weight of all synthesized compounds was recorded on GCMS Agilent Technologies 7890 A (GC System). The Agilent Technologies used was 5975C inert XLEI/CI MSD with Triple-Axis Detector. 1H and 13C nuclear magnetic resonance spectra were recorded using JEOL NMR spectrometer instrument operating at 400 MHz and 100 MHz, respectively.

Procedure for the synthesis of 1-substituted β-carbolines (4a-g)

To a stirred mixture of 5-hydroxy-L-tryptophan (1.3 equiv.) in *p*-toluene sulfonic acid monohydrate (*p*-TsOH.H_2O) (1.0 equiv.) and selected glyoxal (1.0 equiv.) in methanol (50 mL) was added. Then, the solution was heated to 50℃ for 4 hours and the presence of glyoxal was monitored by TLC analysis until it was completely consumed. The reaction mixture was poured into water and the precipitate was filtered and purified by silica gel column chromatography eluted with a gradient of acetone and petroleum ether (1:1) to obtain the desired 1-substituted β-carboline products **4a-g**.

(6-hydroxy-9H-pyrido[3,4-b]indol-1-yl)(4-methoxyphenyl)methanone (4a). Yield 25%, brown solid. mp 185-186 °C. ^{1}H NMR (CD_3OD, 400 MHz): 11.98 (1H, br s, NH), 9.20 (1H, br s, OH), 8.52 (1H, d, H-3), 8.41 (1H, d, H-4), 8.31 (2H, d, H-2' and H-6'), 8.30 (1H, d, H-5), 7.79 (1H, d, H-8), 7.59 (1H, dd, H-7), 7.10 (2H, d, H-3' and H-5'), 3.87 (3H, s, OCH3);^{13}C NMR (CD_3OD, 100 MHz): δ 163.5, 151.5, 136.8, 136.1, 135.9, 133.8, 136.5, 44 130.0, 121.2, 118.7, 117.9, 112.2, 105.5, 100.3, 54.6. IR V_{max} cm^{-1}: 3492, 3432, 1642, 1621. MS *m/z*: calculated for $C_{19}H_{14}N_2O_3$, (M+ 288.01) found (M^+ 288.04).

(6-hydroxy-9H-pyrido[3,4-b]indol-1-yl)(phenyl)methanone (4b). Yield 43%, yellow solid. mp 135-136 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 12.06 (1H, br s, NH), 9.22 (1H, br s, OH), 8.53 (1H, d, H-3), 8.46 (1H, d, H-4), 8.33 (1H, d, H-5), 8.18 (2H, d, H-2' and H-6'), 7.81 (1H, d, H-8), 7.69–7.55 (4H, m, H-7, H-3', H-4', and H-5'). ^{13}C NMR (CD_3OD, 100 MHz): δ 191.8, 163.0, 141.8, 137.2, 137.1, 135.9, 133.6, 131.0, 130.0, 129.0, 122.0, 120.3, 118.6, 113.6, 113.1, 55.7. IR V_{max} cm^{-1}: 3500, 3423, 1697. MS *m/z*: calculated for $C_{18}H_{12}N_2O_2$, (M^+ 318.15) found (M^+ 318.16).

(6-hydroxy-9H-pyrido[3,4-b]indol-1-yl)(4-hydroxyphenyl)methanone (4c). Yield 30%, light brown solid. mp 155-156 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 12.18 (1H, br s, NH), 9.68 (1H, br s, OH), 9.23 (1H, br s, OH), 8.68 (1H, d, H-3), 8.51 (1H, d, H-4), 8.43 (2H, d, H-2' and H-6'), 8.32 (1H, d, H-5), 7.87 (1H, d, H-8), 7.52 (1H, dd, H-7), 7.12 (2H, d, H-3' and H-5'); ^{13}C NMR (CD_3OD, 100 MHz): δ 170.8, 165.0, 143.9, 138.2, 136.1, 135.2, 133.2, 131.8, 130.0, 129.0, 122.0, 120.8, 118.4, 113.6, 114.5. IR V_{max} cm^{-1}: 3499, 3456, 1678. MS *m/z*: calculated for $C_{18}H_{12}N_2O_3$, (M^+ 304.03) found (M^+ 304.09).

(6-hydroxy-9H-pyrido[3,4-b]indol-1-yl)(4-nitrophenyl)methanone (4d). Yield 52%, brown solid. mp 194-196 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 12.09 (1H, br s, NH), 9.19 (1H, br s, OH), 8.51 (1H, d, H-3), 8.44 (1H, d, H-4), 8.31 (1H, d, H-5), 8.15 (2H, d, H-2' and H-6'), 7.82 (1H, d, H-8), 7.81 (2H, d, H-3' and H-5'), 7.60 (1H, t, H-7); ^{13}C NMR (CD_3OD, 100 MHz): δ 192.8, 141.9, 137.4, 136.6, 136.0, 133.0, 131.3, 131.2, 129.2, 126.5, 122.0, 120.4, 120.2, 119.3, 113.2. IR V_{max} cm^{-1}: 3443, 3389. MS *m/z*: calculated for $C_{18}H_{11}N_3O_4$, (M^+ 333.01) found (M^+ 333.06).

(4-bromophenyl)(6-hydroxy-9H-pyrido[3,4-b]indol-1-yl)methanone (4e). Yield 45%, dark brown solid. mp 194-196 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 12.09 (1H, br s, NH), 9.19 (1H, br s, OH), 8.51 (1H, d, H-3), 8.44 (1H, d, H-4), 8.31 (1H, d, H-5), 8.15 (2H, d, H-2' and H-6'), 7.82 (1H, d, H-8), 7.77 (2H, d, H-3' H-5'), 7.60 (1H, t, H-7); ^{13}C NMR (CD3OD, 100 MHz): δ 192.8, 141.9, 137.4, 136.6, 136.0, 133.0, 131.3, 131.2, 129.2, 126.5, 122.0, 120.4, 120.2, 119.3, 113.2. IR V_{max} cm^{-1}: 3443, 3389. MS *m/z*: calculated for $C_{18}H_{11}BrN_2O_2$, (M^+ 367.02) found (M^+ 367.04).

(3,4-difluorophenyl)(6-hydroxy-9H-pyrido[3,4-b]indol-1-yl)methanone (4f). Yield 49%, brown solid. mp 194-196 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 12.09 (1H, br s, NH), 9.19 (1H, br s, OH), 8.51 (1H, d,

H-3), 8.44 (1H, d, H-4), 8.31 (1H, d, H-5), 8.20 (1H, d, H-6'), 7.90 (1H, d, H-2') 7.82 (1H, d, H-8), 7.47 (1H, d, H-5'), 7.60 (1H, t, H-7); ^{13}C NMR δ (CD_3OD, 100 MHz): 192.8, 141.9, 137.4, 136.6, 136.0, 133.0, 131.3, 131.2, 129.2, 126.5, 122.0, 120.4, 120.2, 119.3, 113.2. IR V_{max} cm^{-1}: 3443, 3389. MS *m/z*: calculated for $C_{18}H_{10}F_2N_2O_2$, (M^+ 324.01) found (M^+ 324.08).

(6-hydroxy-3-(hydroxymethyl)-9H-pyrido[3,4-b]indol-1-yl)(4hydroxyphenyl)methanone (4g). Yield 46%, dark brown solid. mp 155-156 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 12.18 (1H, br s, NH), 9.68 (1H, br s, OH), 9.23 (1H, br s, OH), 8.68 (1H, s, H-4), 8.51 (1H, d, H-5), 8.43 (1H, d, H-6'), 8.32 (1H, d, H-2'), 7.87 (1H, d, H-8), 7.52 (1H, d, H-7), 7.12 (1H, d, H-3' H-5'), 5.27 (2H, s, H-3); ^{13}C NMR δ (CD_3OD, 100 MHz): 170.8, 165.0, 143.9, 138.2, 136.1, 135.2, 133.2, 131.8, 130.0, 129.0, 122.0, 120.8, 118.4, 113.6, 114.5, 57.2. IR V_{max} cm^{-1}: 3499, 3456, 1678. MS *m/z*: calculated for $C_{19}H_{14}N_2O_4$, (M^+ 334.40) found (M^+ 334.47).

Anti-inflammatory Activity

Xanthine Oxidase (XO) Inhibitory Assay

All compounds **4a-f** were evaluated for anti-inflammatory activity using the xanthine oxidase (XO) inhibitory assay. The XO activities using xanthine as the substrate were measured spectrophotometric ally, followed Noro *et al*. (1983) technique [15]. The assay mixture consisted of 1.0 mL of test solution, 2.9 mL of 1/15 M phosphate buffer (pH 7.5) and 0.1 mL of enzyme solution. After preincubating the mixture at 25 °C for 15 minutes, the reaction was started by adding 2.0 mL of substrate solution. This assay mixture was incubated at 25 °C for 30 minutes. The reaction was then stopped by adding 1 mL of 1 N HCl, and the absorbance of the assay mixture was measured using spectrophotometer at 290 nm. The blank was prepared in the same way, but the enzyme solution was added to the assay mixture after adding 1 N HCl. One unit of XO was defined as the amount of enzyme producing 1 µmol of uric acid per min at 25 °C.

Estimation of Xanthine Oxidase (XO) Inhibitory Activity

XO inhbitory activity was expressed as the percentage of inhibition of XO in the above assay system, calculated as

$$(1\text{-}B/A) \times 100\%$$

where A is the activity of the enzyme without test material and B is the activity of the enzyme with test material.

Results and Discussion

As previously mentioned, this method has been a prominent focus of research throughout the years, with scientists constantly refining the methodology and introducing novel reaction conditions. It is interesting to note that under modified Pictet-Spengler conditions, a convenient one-step conversion of tryptophan derivatives and aldehydes directly to β-carbolines without generating tetrahydro intermediates has been described. The simplicity of this one-pot oxidation procedure prompted us to explore the scope and synthesis of a range of 1-substituted β-carboline derivatives. Thus, we came across to report the continuous investigation from Asha'ri *et al*., 2022 in synthesizing the naturally occurring 1-substituted β-carboline derivatives **4a-g**, using 5-hydroxy-L-tryptophan as the starting material with activated phenylglyoxal.

By virtue of the readily synthetic availability, 5-hydroxy-L-tryptophan was chosen as the model substrate. The one-pot reaction commencing with the L-tryptophan and different substituted phenylglyoxal. The addition of *p*-TsOH.H_2O in the mixture act as a catalyst in methanol solvent were stirred and furnishing the product **4a-g** (Scheme 1). Finally, the crude 1-substituted β-carbolines were purified via column chromatography to obtain 1-substituted-β-carboline **4a-g** from low to moderate yields. Compounds **4a-d** and **4g** are previously known, whereas **4e-f** are newly synthesized compounds. The structures of all synthesized compounds were validated using ^{1}H- and ^{13}C-NMR, FTIR, and MS spectroscopic data.

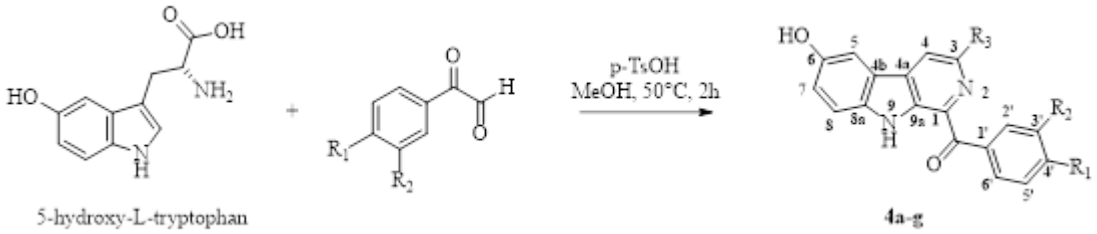


Figure 3. Synthesis of 1-substituted-β-carboline, **4a-g**

Table 1. Reaction conditions for synthesis of compound **4a-g**

Compound	R1	R2	R3	Yields (%)
4a	OCH_3	H	H	25
4b	H	H	H	43
4c	OH	H	H	30
4d	NO_2	H	H	52
4e	Br	H	H	45
4f	F	F	H	49
4g	OH	H	CH_2OH	46

By employing the Pictet-Spengler condensation, we only managed to get the derivatives of 1-substituted β-carbolines **4a-g** in low to moderate yields, from 25% to 52%, respectively. Compounds **4a** and **4c** gave poor yields compared to compounds **4d** and **4f,** which have higher yields. Moderate yield was observed for compounds **4b**, **4e**, and **4g**. This is due to the substituents attached to the phenylglyoxal and is reactive towards the nucleophilic addition because the bonds between the carbon and hydrogen can easily break. Not for the aromatic glyoxal are less reactive towards the nucleophilic addition reaction because the bonds are strong stabilized by carbon ring.

As shown in Table 1, aromatics bearing electron-withdrawing group (EWG) provide a higher yield than those with an electron-donating group (EDG). This can be explained by the inductive and resonance effects of the substituents. The EDG will donate their electron by increasing the electrophilicity of the carbonyl carbon, resulting in a weaker reactivity with the nucleophile and thus, low percentage yield. The OCH_3 substituent is a stronger EDG than OH substituents, resulting in a lower yield compared to **4c**. In contrast to weak EWG, **4e** and **4f** were shown to have better yields compared to unsubstituted **4b**, but poor yield than strong EWG of **4d**. This might be due to weak EWGs slightly stabilize the intermediate states during the synthesis process, making the reaction more efficient and resulting in a better yield compared to the unsubstituted compound. However, because the electron-withdrawing effect in **4e** and **4f** is not as strong as in **4d**, the stabilization is limited, which restricts the yield improvement compared to compound **4d**.

All the synthesized compounds were tested against xanthine oxidase for their anti-inflammatory assessment. The results of inhibitory activity of the respective derivatives of 1-substituted β-carbolines are shown in Table 2.

Table 2. Anti-inflammatory activity of 1-substituted β-carboline derivatives

Compound	Inhibition [%]
4a	32.17 ± 1.97
4b	48.33 ± 1.13
4c	15.92 ± 4.99
4d	58.03 ± 0.31
4e	47.24 ± 2.85
4f	24.65 ± 2.97

As reported, β-carbolines are known for their diverse biological activities, including anti-inflammatory properties [17]. In the context of anti-inflammatory activity, one of the mechanisms through which β-carbolines exert their effects is by inhibiting enzymes involved in inflammatory processes, such as xanthine oxidase (XO). Xanthine oxidase is a key enzyme involved in the production of reactive oxygen species (ROS) and free radicals, which contribute to inflammatory response [18,19]. By inhibiting xanthine oxidase activity, β-carbolines can help reduce the levels of ROS and free radicals, thereby mitigating the inflammatory cascade as well as highlighting their potential therapeutic applications in inflammatory disorders [20].

From the observation, all the compounds tested showed anti-inflammatory activities against xanthine oxidase, ranging from weak to moderate inhibitory effects. Of the compounds tested, only three compounds, 4b, 4d, and 4e demonstrated moderate inhibition of xanthine oxidase, with percent inhibition ranging from 40% to 70%. Among these, 4d had the strongest inhibitory effect, with a 58.03% inhibition rate. Meanwhile, compounds **4a**, **4c**, **4f** and **4g** showed weak activity towards the enzyme which the percent inhibition is lower than 40% [21]. It was observed that compound **4c**, which contains hydroxyl substituents, exhibited minimal inhibition of xanthine oxidase. In contrast, compounds with electrophilic substituents, such as bromo and nitro groups, demonstrated a better inhibitory effect on xanthine oxidase, as seen in compounds **4d** and **4e** [16].

Conclusions

In summary, the 1-substituted glyoxal β-carboline was successfully synthesized using direct Pictet-Spengler condensation of 5-hydroxy-L-tryptophan with selected phenylglyoxal. The percentage yield of compounds **4a** (25%), **4b** (43%), **4c** (30%), **4d** (52%), **4e** (45%), **4f** (49%) and **4g** (46%) varies depending on the substituent connected to the phenyl. Compounds with EDG have low yields, whereas the EWG provide better yields. This alternative is improved since the synthesis reaction is simple and straightforward without the intermediate formation of tetrahydro-β-carboline by utilizing *p*-TsOH.H_2O as the catalyst. All compounds were successfully evaluated for their anti-inflammatory activities against xanthine oxidase, ranging from weak to moderate inhibitory effect. The nitro substituents exhibit better inhibition than the others. Future in vitro investigations on **4a-f** can be done so that more biological potential can be discovered.

Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Acknowledgement

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References

[1] Dai, J., Dan, W., Schneider, U., & Wang, J. (2018). β-Carboline alkaloid monomers and dimers: Occurrence, structural diversity, and biological activities. *European Journal of Medicinal Chemistry, 157*, 622–656.

[2] Ashari, N. A. N., Pungot, N. H., Jani, N. A., & Shaameri, Z. (2022). Efficient synthesis of novel 1-substituted β-carboline derivatives via Pictet-Spengler cyclization of 5-hydroxy-L-tryptophan. *Malaysian Journal of Fundamental and Applied Sciences, 18*(2), 218–226.

[3] Ash'ari, N. A. N., Pungot, N. H., Shaameri, Z., & Jani, N. A. (2021). A facile synthesis of n-alkylated daibucarboline A derivatives via Pictet-Spengler condensation of tryptamine. *Malaysian Journal of Analytical Sciences, 25*(5), 706–715.

[4] Farzin, D., & Mansouri, N. (2006). Antidepressant-like effect of harmane and other β-carbolines in the mouse forced swim test. *European Neuropsychopharmacology, 16*(5), 324–328.

[5] Zhou, S., Huang, G., & Chen, G. (2021). Synthesis and anti-tumor activity of marine alkaloids. *Bioorganic & Medicinal Chemistry Letters, 41*, 128009.

[6] Nikam, T. D., Nitnaware, K. M., & Ahire, M. L. (2013). Alkaloids derived from tryptophan: Harmine and related alkaloids. *Natural Products: Phytochemistry, Botany and Metabolism of Alkaloids, Phenolics and Terpenes* [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg, 553–574.

[7] Mayser, P., Schäfer, U., Krämer, H. J., Irlinger, B., & Steglich, W. (2002). Pityriacitrin–an ultraviolet-absorbing indole alkaloid from the yeast *Malassezia furfur*. *Archives of Dermatological Research, 294*, 131–134.

[8] Nagao, T., Adachi, K., Nishida, F., Nishishima, M., Mochida, K., Nagao, T., & Mochida, K. (1999). New

ultraviolet-absorbing substance produced by marine bacteria and its production. *JP Patent, 11*, 269, 175.

[9] Liew, L. P., Fleming, J. M., Longeon, A., Mouray, E., Florent, I., Bourguet-Kondracki, M. L., & Copp, B. R. (2014). Synthesis of 1-indolyl substituted β-carboline natural products and discovery of antimalarial and cytotoxic activities. *Tetrahedron, 70*(33), 4910–4920.

[10] Almeida, M. C., Resende, D. I., da Costa, P. M., Pinto, M. M., & Sousa, E. (2021). Tryptophan derived natural marine alkaloids and synthetic derivatives as promising antimicrobial agents. *European Journal of Medicinal Chemistry, 209*, 112945.

[11] Zhu, L. H., Chen, C., Wang, H., Ye, W. C., & Zhou, G. X. (2012). Indole alkaloids from *Alocasia macrorrhiza*. *Chemical and Pharmaceutical Bulletin, 60*(5), 670–673.

[12] Zulkifli, S. Z., Pungot, N. H., Saaidin, A. S., Jani, N. A., & Mohammat, M. F. (2023). Synthesis and diverse biological activities of substituted indole β-carbolines: A review. *Natural Product Research, 1–14.*

[13] Shamsujunaidi, R., Saaidin, A. S., Aziz, M. H. A., Mohammat, M. F., & Pungot, N. H. (2023). Studies on the synthesis of β-carboline and its derivatives as potential antimalarial drug components. *Malaysian Journal of Analytical Sciences, 27*(1), 44–53.

[14] Kirsch, G., König, G. M., Wright, A. D., & Kaminsky, R. (2000). A new bioactive sesterterpene and antiplasmodial alkaloids from the marine sponge *Hyrtios cf. erecta*. *Journal of Natural Products, 63*(6), 825–829.

[15] Noro, T., Oda, Y., Miyase, T., Ueno, A., & Fukushima, S. (1983). Inhibitors of xanthine oxidase from the flowers and buds of *Daphne genkwa*. *Chemical and Pharmaceutical Bulletin, 31*(11), 3984–3987.

[16] Ishibuchi, S., Morimoto, H., Oe, T., Ikebe, T., Inoue, H., Fukunari, A., *et al.* (2001). Synthesis and structure–activity relationships of 1-phenylpyrazoles as xanthine oxidase inhibitors. *Bioorganic & Medicinal Chemistry Letters, 11*(7), 879–882.

[17] Kumar, B. K., Sekhar, K. V. G., Kunjiappan, S., Jamalis, J., Balaña-Fouce, R., & Sankaranarayanan, M. (2021). Recent update on the anti-infective potential of β-carboline analogs. *Mini Reviews in Medicinal Chemistry, 21*(4), 398–425.

[18] Chelombitko, M. A. (2018). Role of reactive oxygen species in inflammation: A minireview. *Moscow University Biological Sciences Bulletin, 73*, 199–202.

[19] Nakai, K., & Tsuruta, D. (2021). What are reactive oxygen species, free radicals, and oxidative stress in skin diseases? *International Journal of Molecular Sciences, 22*(19), 10799.

[20] Ayipo, Y. O., Mordi, M. N., Mustapha, M., & Damodaran, T. (2021). Neuropharmacological potentials of β-carboline alkaloids for neuropsychiatric disorders. *European Journal of Pharmacology, 893*, 173837.

[21] Elbestawy, M. K., El-Sherbiny, G. M., Moghannem, S. A., & Farghal, E. E. (2023). Antibacterial, antibiofilm, and anti-inflammatory activities of ginger extract against *Helicobacter pylori*. *Microbiology Research, 14*(3), 1124–1138.